Exploration of the Reactivity of a Cyclic Vinylogous Ester and Tandem Cascade Sequence Toward the Flavonoid Core Structure

By

Seth Chase Alexander

Honors Thesis

Presented to Dr. Stephen F. Martin

and the Dean's Scholars Honors Committee

in Partial Fulfillment

of the Requirements

for the Degree of

Bachelor of Science in Biochemistry with Honors

The University of Texas at Austin

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Stephen F. Martin, Supervisor

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Seth Chase Alexander, B.S.

University of Texas at Austin, 2008

SUPERVISOR: Stephen F. Martin

I. Abstract

The Heck coupling reaction is a well known and synthetically useful reaction involving the coupling of an aryl halide or aryl triflate with a substituted alkene via a palladium metal catalyst to make a new carbon-carbon bond. This reaction was demonstrated by R.F. Heck in the early 1970's, and soon took a stronghold as a key reaction in synthetic chemistry. There are numerous variations on Heck chemistry, and this area of chemical space has been explored with a variety of substrates. One class of substrates that have yet to be reported in the literature are vinylogous esters (R-O-CH=CHCOR'). These substrates have a very unique electronic environment for the alkene group undergoing the Heck coupling. It is the purpose of this thesis to explore the reactivity of a cyclic vinylogous ester useful in the synthesis of flavonoids; a large class of biologically relevant molecules. The skeletal core of some flavonoids (**Scheme 4**) could be easily accessed through a Heck reaction between a o-allylaryl halide and cyclic vinylogous ester followed by a tandem cyclization step fashioned from a stalled intermediate of the initial

Heck coupling as illustrated in **Scheme 14**. Initial coupling attempts of **14** with **15** failed with recovery of starting material.

A small variety of conditions were explored with little success which led toward a model study of 2-bromotoluene with the cyclic vinylogus ester. Reaction conditions were optimized based upon a screening of solvents, bases, and catalytic species found prevalent in the literature. The results of the model study concluded a 50% conversion to the desired product. When these conditions were applied to the tandem sequence, **14** had partially isomerized to bring the olefin into conjugation with the arene**,** and **15** was recovered with no desired product found in the reaction mixture. It was also found that a narrow range of temperatures was required to balance competing product formation and thermal decomposition. These results therefore conclude that the tandem sequence was not able to be demonstrated. Further, vinylogous esters are weak substrates for Heck coupling reactions most likely due to their electronic delocalization of the alkene π electrons and unique electronic nature. It is felt that this chemistry is heavily substrate dependant, and thus the desired scope of methodology involving vinylogous esters as Heck coupling partners yields a narrow chemical space of successful reactivity due to the high substrate dependence of the Heck reaction.

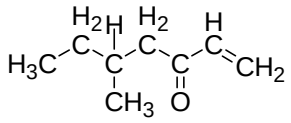
II. Background

Synthetic organic chemistry lies at the cornerstone of all organic chemistry as it is the study of how organic compounds are made. This field proves most useful in providing access to compounds which have been discovered in nature. These natural products are the primary target of synthetic methods and are vital as they provide scaffolds and structures which have been found to have various biological activities that can be applied to new drug development. Methodologies are developed by synthetic chemist to address the question of how these challenging chemical structures can be made from cheap abundant compounds. It is the aim of this thesis to explore one such methodology that could prove useful in accessing the core structure of the flavonoid class of natural products under mild conditions.

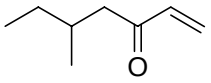
Vocabulary of Organic Chemists

Before addressing such questions, it is important to have a common knowledge of basic chemical principles such that meaningful arguments can be made concerning the nature of the chemistry presented. Organic chemistry is the study of carbon, and thus the ways structures are drawn "short hand" are impossible to decipher without a short explanation of meaning. Carbon is always at each point where two or more lines intersect, and each line represents a single bond. Carbon is known to be tetravalent (having four substitutents) and as is common in nature, Hydrogen is assumed to be present on carbon so that each carbon atom has 4 substituents around it. All other elements (heteroatoms) are identified in the structure by their element symbol in the short hand form. **Scheme 1** represents a small organic molecule written out with each element identified (**1)**, and **2** is expressed in the common short hand.

Scheme 1



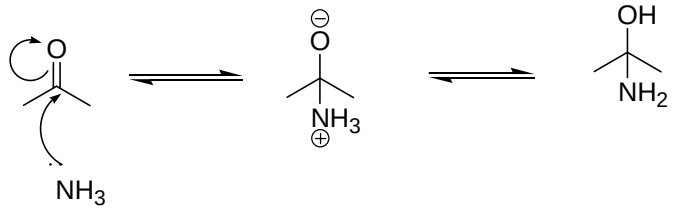
1



2

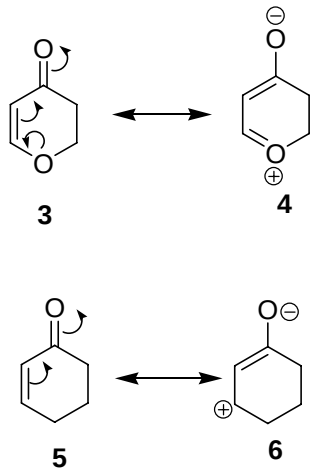
Drawing upon general chemistry principles of oppositely charged chemicals forming associations (think of Na^+ and Cl^- forming NaCl – table salt), organic molecules having slight (+) and (-) regions of the structure (known as dipoles) can form covalent bonds by donating electron pairs from a (-) rich region (electron rich nucleophiles) to a (+) rich region (electron deficient electrophiles). Therefore regions which are highly nucelophilic can "attack" electrophilic regions and form bonds. The flow of electron pairs is thus tracked when drawing out mechanisms by arrows representing electron pairs flowing from the nucleophile to the electrophile. This is a great oversimplification of course, but for the purpose of establishing an understanding of the language involved in arrow pushing, such an explanation is sufficient. An example of arrow pushing is demonstrated below in **Scheme 2** where a nitrogen nucleophile is adding into a carbonyl group. The mechanism is oversimplified and proton transfers are left out; however it does represent the basic principle of arrow pushing so that one can gain an understanding for the short-hand language used in organic chemistry.

Scheme 2



Keeping in mind that all steps are usually reversible and that the short hand is a useful way to discuss the chemical transformations, one can then introduce specific reaction mechanism and thus be able to define and explain methodology based upon studied chemical behavior. These chemical behaviors are usually classified into smaller structures known as functional groups. These groups have unique electronic environments (where the electrons are and how they behave), and thus this gives rise to unique possible chemical transformations for each group. A more in depth explanation of functional group behavior and related reactivity is discussed in undergraduate organic texts[1]. For the purposes of this thesis it is important to understand α,β-unsaturated enones and ester functionality. The vinylogous ester is a functional group that resembles a hybrid of enone and ester functionality by having the double bond between the carbonyl and oxygen as demonstrated in **Scheme 3** below. This yields a unique electronic environment which has resonance structures that might help predict the electronic nature of the double bond of the vinylogous ester which is to be reacted in the heck reaction proposed. Oxygen lone pair donation may aid in stabilizing the enolate resonance thus decreasing the true olefin (carbon carbon double bond) character of the alkene in this system. This resonance as shown by the resonance of **3** with **4** demonstrates that the β position is less positive than in an α,β unsaturated enone demonstrated by the resonance of **5** with **6**.

Scheme 3

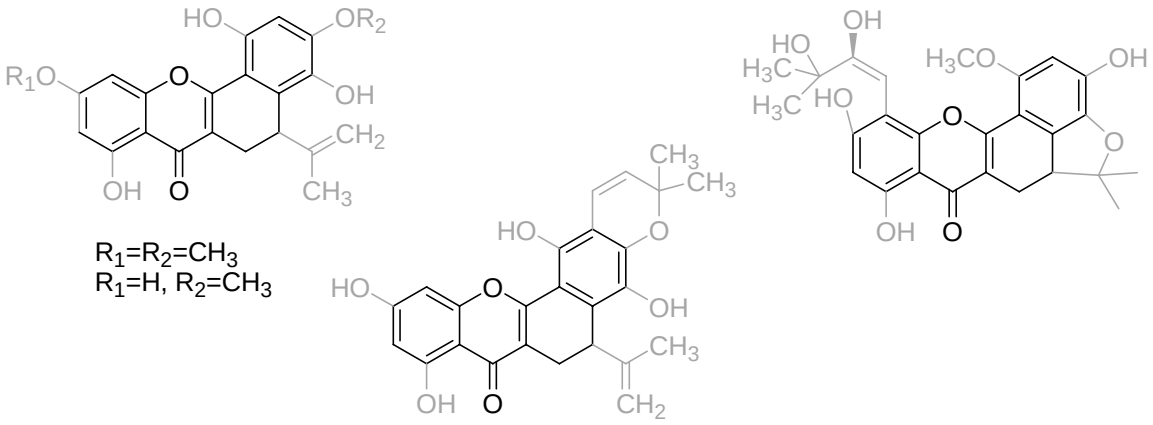


With these principles in mind, one begins to be able to discuss the project undertaken in this thesis.

Project Outline and Background

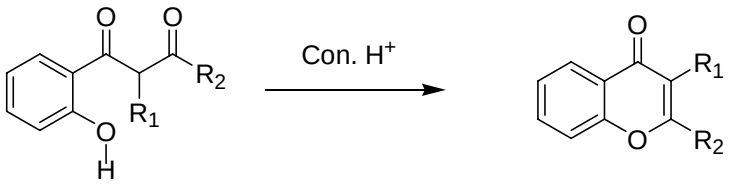
Flavonoids are a large class of natural products which have been isolated from nature. These compounds have been widely explored and many compounds of this class are known to have biological activity including antioxidant properties[2]. It is therefore useful to develop methodology that provides easy access to compounds with the core structure of flavonoids. Examples of biologically relevant flavonoids are shown in **Scheme 4** with the common core structure highlighted[2-4].

Scheme 4



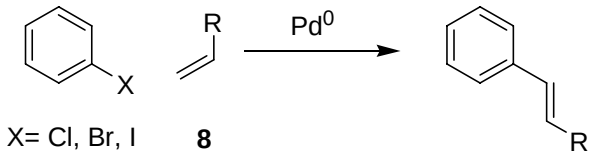
Common current methods to access the core structure of flavonoids require a harsh acidic environment as demonstrated in **Scheme 5**[5,6]. It therefore seems useful to develop methodology that would easily access flavonoid natural products using more mild conditions. One such approach proposed herein utilizes a well known reaction: the Heck reaction.

Scheme 5



The Heck Reaction was first reported in the early 1970's independently by Mizoroki and Heck[7,8]. The reaction is broadly defined as a coupling between an aryl halide (**7**) and an alkene (**8**) via a palladium(0) metal catalyst.

Scheme 6

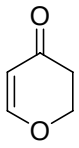


X= Cl, Br, I **8**

7

This reaction has been heavily studied and has proven to be a highly useful synthetic tool for the formation of carbon-carbon bonds between the two functional groups involved[9]. One type of alkene that has not been reported in the literature to undergo a Heck coupling reaction is a Vinylogous Ester (**9)**.

Scheme 7



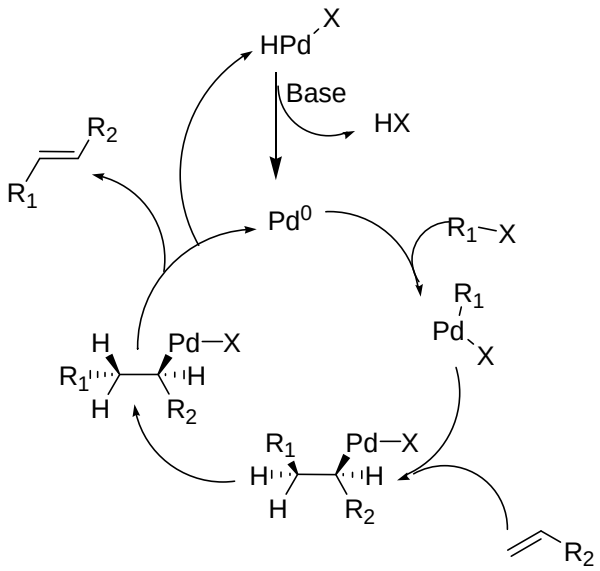
9

This core structure is found in the flavonoid class of natural products as discussed previously, and thus incorporation of **9** into flavonoid synthesis via mild Heck Chemistry would demonstrate an alternative to the harsh acidic conditions previously employed.

Before outlining the exact details of how Heck chemistry can be applied to the synthesis of Flavonoid core structures, it is important to critically discuss the mechanism behind the Heck catalytic cycle. Although well studied, the Heck reaction is extremely complex as there is significant controversy over the exact catalytic cycle employed by the reaction[10]. In fact, there are multiple pathways proposed such as neutral, cationic, and anionic pathways which can

dominated based upon the conditions chosen[11]. The generally accepted catalytic cycle is shown below in **Scheme 8**[11].

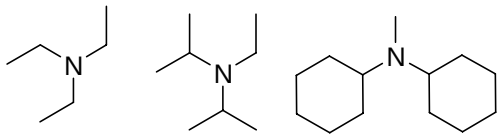
Scheme 8



Palladium metal serves as the key catalytic device which allows the desired carbon-carbon bond to be made in the Heck Reaction. The Palladium must begin the cycle in its zero-valent metal oxidation state. This state is unstable in solution and requires ligands to coordinate around the palladium to hold the metal in the Pd^0 state. It is important to recognize that ligands must coordinate to the palladium species to hold it in solution such that it can undergo the desired catalytic cycle. In fact, one issue with the Heck reaction is the formation of palladium black which has crashed out of solution and is non recoverable nor able to further catalyze the reaction. While some ligands coordinating to metals change the oxidation state of the metal, others simply share electron density such that the metal is stabilized in solution. The number of ligands bound to Pd is transient and largely disputed and unknown[10]. Palladium(0) is typically made within the reaction vessel at time of reaction by a reduction of Pd^{II} (palladium in the +2

oxidation state) to Pd^0. This is achieved by amine base reduction or phosphine reduction, and an addition of coordinating ligands which do not contribute to the formal oxidation state of the metal species, but rather only stabilize the zero valent metal. The reduction of Pd^{II} to Pd^0 is typically done with a phosphine ligand such as triphenyl phosphine, and therefore it is necessary to add an extra equivalent of phosphine ligand to be consumed during Pd^0 formation[11]. Basic (high pH) conditions are necessary for catalyst regeneration, and therefore K_2CO_3 or an amine base such as triethylamine – $(C_2H_5)_3N$ (**10**) ,Hünig's base - $(i\text{-}Pr)_2NEt$ (**11)**, or dicyclohexylmethylamine – Cy_2NMe (**12**) is typically added in excess. The structures of these bases are shown below in **Scheme 9**. Choice of base is critical because the base can also serve as a ligand on the Pd species, and thus the "bulkyness" of base can play a role in how the Pd species behaves in solution[9].

Scheme 9

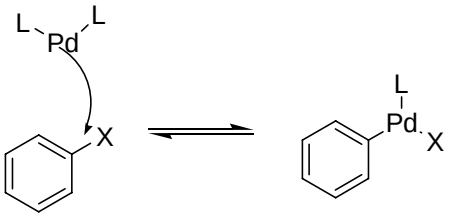


10 **11** **12**

Once Pd^0 is present in solution, it will coordinate and "oxidativly add" into an aryl halide bond. The term oxidative addition is typically used which implies that the formal oxidation state of palladium goes from Pd^0 to Pd^{II} (a net oxidation of the catalyst) when inserting between the carbon atom of the aromatic ring and halogen atom. This step is widely regarded as a common rate limiting step; meaning that this is the most difficult transformation within the catylitic cycle[11]. However, it is critical to realize that multiple steps throughout the cycle can become the

rate limiting step based upon not only the reaction conditions, but the two Heck partners chosen. An oversimplified illustration of oxidative addition step is shown below in **Scheme 10**.

Scheme 10

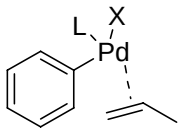


X=Halogen (Cl, Br, I)

Once the palladium has undergone oxidative addition into the C-X bond, the formal oxidation state of palladium is now +2. This change in oxidation implies reduction has also occurred (at the carbon atom previously bearing the halide), and one can think of the carbon now bearing the palladium species to be nucleophilic and thus able to "attack" electrophiles.

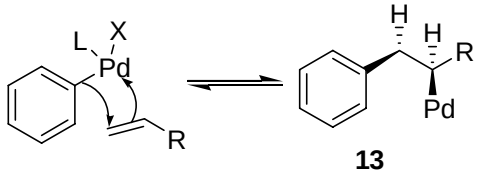
The next step in the catalytic cycle involves the palladium intermediate coordinating with an alkene. The electronic state of a carbon – carbon double bond has π orbitals filled with electrons which can coordinate with palladium bringing the carbon nucleophile within proximity of the alkene. The π orbitals can be thought of as large dumbbell shape "lobes" which extend away perpendicular to the carbon atoms of the C-C double bond, and thus can physically overlap with the electrons of palladium forming what is known as a "dative" bond. This is illustrated in **Scheme 11**.

Scheme 11



The next step of the catalytic cycle is known as alkene insertion, whereby the alkene inserts itself between the carbon-Pd bond. This can be simplified by thinking of the carbon nucleophile attacking the alkene, and the palladium species transferring itself onto the other carbon atom involved in the C-C double bond. Regioselectivity is substrate specific and heavily depends upon the electronics of the C-C double bond and product stability[10]. In the case of enones however, the C-C bond formed is at the more electropositive β-position[12]. This implies that upon alkene insertion the carbon carbon bond is typically made at the site of greater (+) charge such that the palladium can be stabilized by enolization. Electron poor alkenes react the best during this step, while electron rich olefins react readily, but at a slower rate[13]. The alkene insertion is known to occur *syn* (meaning from the same side) and thus there is no hydrogen atom on the same side adjacent to the Pd species for elimination (**13**); a key component of the Heck Reaction. A simplified mechanism is shown in **Scheme 12**.

Scheme 12

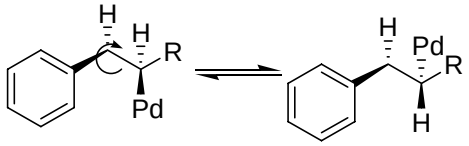


13

The next step of the catalytic cycle requires the palladium species and an adjacent hydrogen to be on the same side for palladium hydride elimination. For this to be possible, free

rotation is required around the C-C bond such that Pd can be *syn* to the adjacent hydrogen as illustrated in **Scheme 13**.

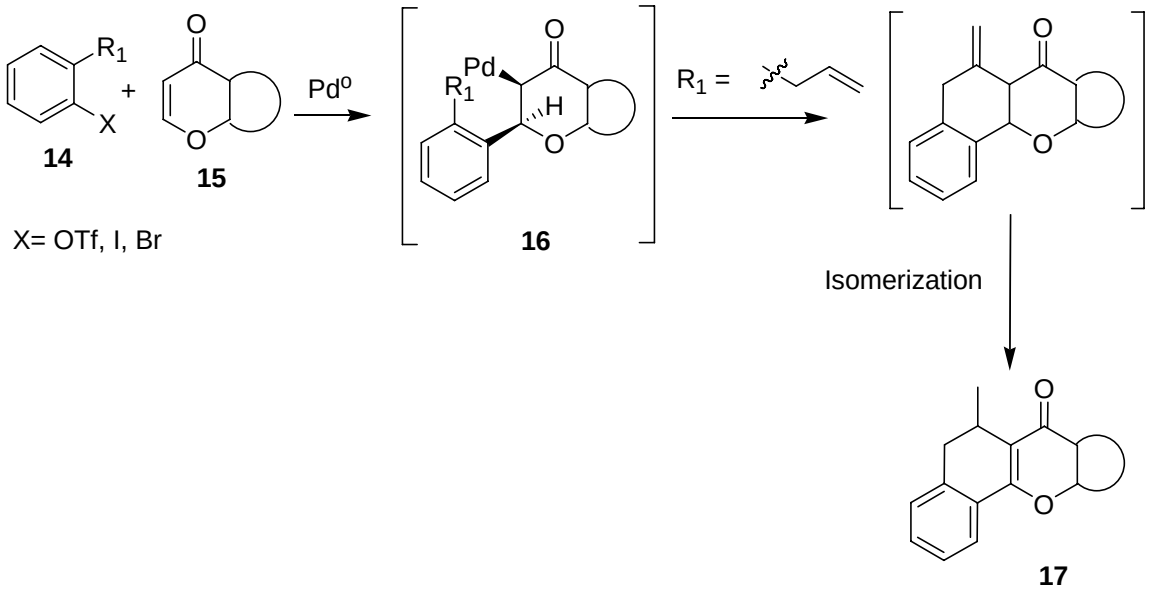
Scheme 13



Once on the same face, palladium and hydrogen can eliminate forming a Pd-H species and alkene with the newly formed C-C bond between the two original Heck coupling partners. The base can then reduce the Pd-H which still has a Pd^{II} oxidation state back to Pd^{0} which can reenter the catalytic cycle. It is thought that the base may play a more direct role in the final Pd-H elimination step, and hence one instance when its bulkyness can have an effect upon the rate of reactivity. This final step of the catalytic process is therefore known as reductive elimination[11].

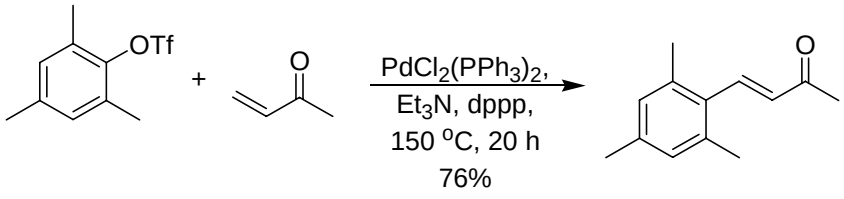
With an understanding of the Heck catalytic cycle, a proposed sequential reaction can be envisioned allowing access to the core structure of flavonoids. As seen in **Scheme 14**, an initial coupling with cyclic vinylogous ester **15** leading to intermediate **16** could then set up a potential secondary "tandem" heck coupling intramolecularly (within the same molecule) yielding the desired core structure of flavonoids. Further, an isomerization could occur resulting in the thermodynamically stable product **17** via residual Pd-H which is known to be able to isomerize double bonds to the thermodynamic isomer. An amine base catalyzed isomerization process could also be envisioned due to the excess base and heat required for the reaction.

Scheme 14



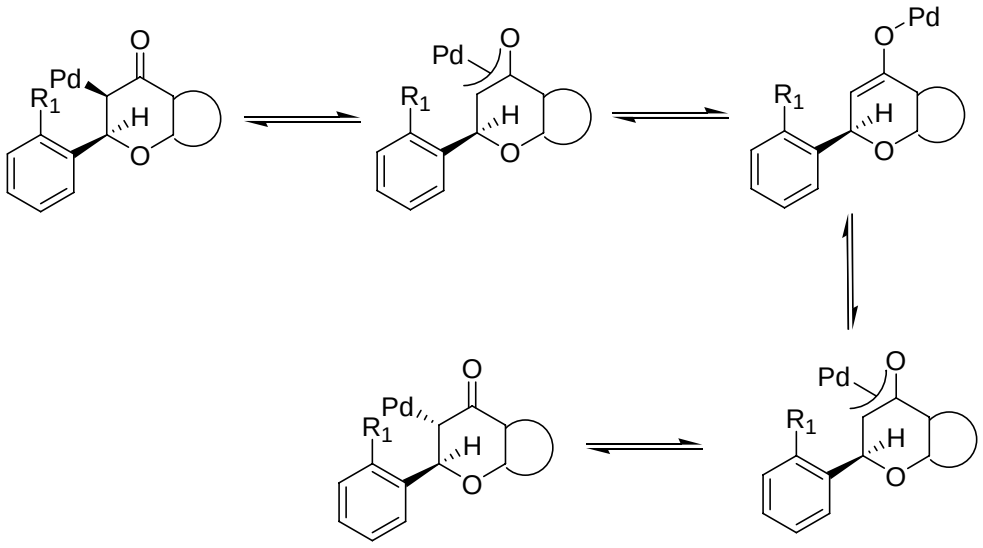
The initial coupling of an aryl halide **14** and vinylogous ester **15** would result in **16**. It is unknown in the literature if the olefin insertion would be in favor of the regiochemistry of **16**; however literature precedent of enones would suggest substitution at the β-carbon as illustrated by Hagiwara, Eda, and Suzuki in **Scheme 15**[12]. It is important to realize that the β-carbon is not as electron poor in a vinylogous ester compared with an enone as previously demonstrated in **Scheme 3**. Therefore, it is important to establish the site of C-C bond formation in vinylogous esters.

Scheme 15



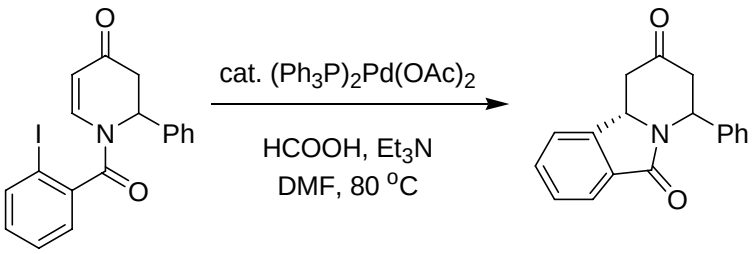
The initial product **16** cannot freely rotate as needed based upon the catalytic cycle necessary for subsequent hydride elimination. This sets up a stalled intermediate which can undergo further chemistry. It is important to realize that this intermediate is not completely stalled. The palladium can enolize as demonstrated in **Scheme 16** and return to the carbon atom on the correct face for a *syn*-elimination**.** This enolization should easily be outcompeted by an intramolecular reaction based upon literature presedent[14], and only if no intramolecular reaction was possible, should this route yield a setup for hydride elimination.

Scheme 16



Literature precedent for vinylogous amides undergoing an intramolecular Heck coupling provides evidence towards the ability of hydride elimination via enolization that would be necessary to complete the reaction outlined in **Scheme 17**[15]. This also provides insight as to the reactivity of a similar partner to the unexplored cyclic vinylogous ester.

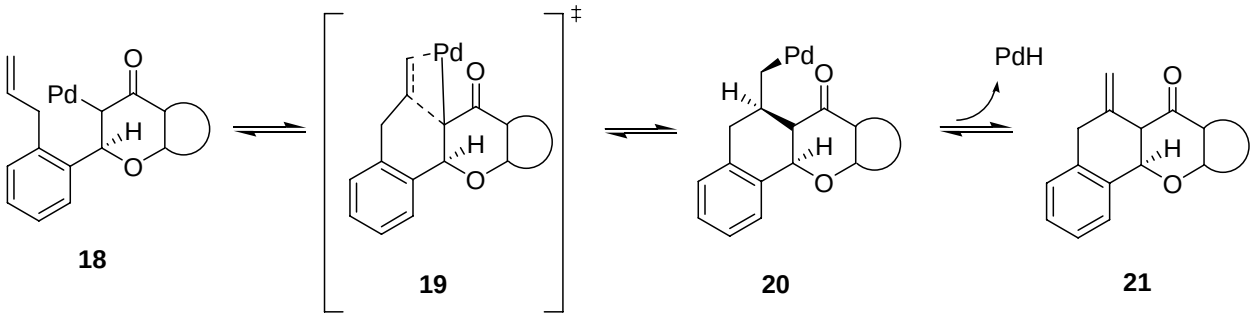
Scheme 17



Literature precedent with tandem sequences such as the one demonstrated by Huang, Q. and Larock, R. L. provides evidence that a tandem intramolecular reaction can occur when hydride elimination is not possible[16] and provides support to a tandem sequence such as the one proposed.

Once initial intermediate **16** is formed, the functionality of R1 can be functionalized such that a second heck coupling is possible within the intermediate. If R1 were allyllic, then the product **17** would result. In this secondary reaction the thermodynamically stable 6 member ring is formed. The intermediate leading to this reaction is shown below in **Scheme 18** where by the palladium of **18** goes through a transition state **19** resulting in the formation of **20.** This compound has a freely rotatable CH_2Pd which can rotate and result in Pd-H elimination resulting in **21**, thus completing the cascade sequence.

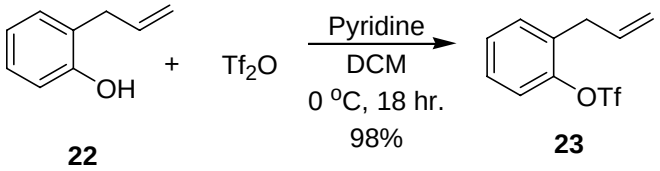
Scheme 18



III. Results and Discussion

To access the route outlined in **Scheme 18**, one must first choose exactly what two partners should be reacted to yield the tandem sequence. 2-allylphenol can be easily converted in one step to the triflate[17]. Not only is the triflate easy to access, but it is well known in the literature to be a good substituent for the oxidative addition step of the catalytic cycle, and has been widely used in several Heck reactions. With this in mind, the triflate derivative of 2-allylphenol was chosen to be the initial partner in the coupling attempt. A reaction of 2-allylphenol (**22**) with triflic anhydride and pyridine in dicholormethane at 0 ^{o}C for 18 hours gave the corresponding triflate **23** in virtually quantitative yields.

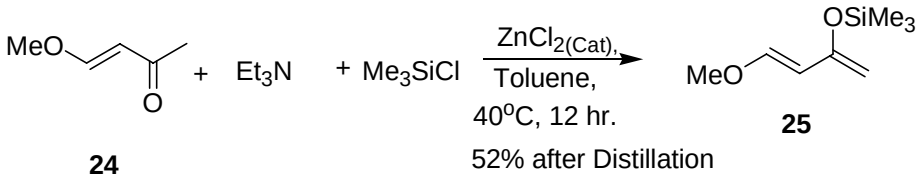
Scheme 19



22 **23**

It was decided for the purpose of exploring reactivity of cyclic vinylogous esters, that 2-phenyl-2,3-dihydro-pyran-4-one was a facile material to make from the hetero Diels Alder reaction of benzaldehyde with Danishefsky's diene[18]. The Diene was synthesized[19] from commercially available 4-methoxy-3-buten-2-one (**24**) and trimethylsilyl chloride utilizing $ZnCl_2$ as a Lewis acid catalyst in Toluene at 40 ^{o}C for 12 hours yielding diene **25** in 52% after distillation.

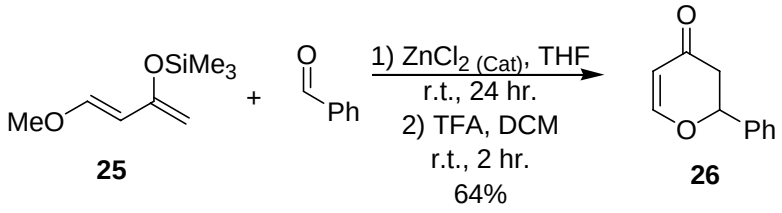
Scheme 20



24 **25**

With diene **25** in hand, the hetero Diels Alder reaction as reported by Danishefsky was then used to obtain the cyclic vinylogous ester[18]. Danishefksy's Diene was combined with benzaldehyde utlizing $ZnCl_2$ as a catalyst in Tetrahydrofuran for 24 hours followed by treatment with Trifluoroacetic acid in Dichloromethane for 2 hours affording 62% of the vinylogous ester **26**.

Scheme 21

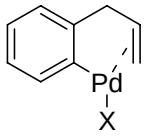


25 **26**

With the starting materials in hand, an initial attempt based upon literature precedent of general conditions for the Heck reaction was explored [14]. A 10 mol% of $Pd(OAc)_2$ with XS PPh_3 utilizing 3 eq. of NEt_3 in acetonitrile at 80 ^oC was first employed to couple the aryl triflate **23** and vinylogous ester **26** without success. Both starting materials were recovered. More importantly, the triflate was recovered, rather than 2-allyl benzene which implies oxidative addition did not occur on the aryl triflate. It is important to note that some oxidative addition did occur, as some 2-allyl benzene was recovered; however only small amounts were seen, and no converted product was observed. Because only trace amounts of allylbenzene was observed, it can be

hypothesized that the allyl group may be interfering with the oxidative addition intermediate. One can envision the palladium, after oxidativly inserting itself into the carbon-oxygen bond, coordinating with the adjacent olefin (**27**) as shown in **Scheme 22**.

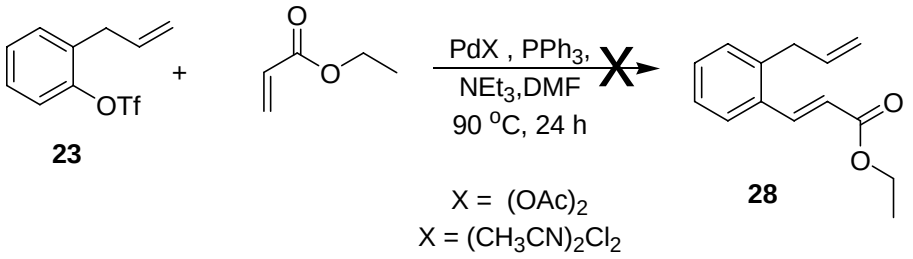
Scheme 22



27

Based upon the initial results, a model system was developed to assess the reactivity of **23** as a Heck partner, such that issues of the observed unreactivity could be overcome. Acrylates are known in the literature to be optimal Heck coupling partners because of their electron withdrawing effects on the olefin [13]. With this in mind, a model study of **23** and ethyl acrylate was employed. The Reaction of **23** with ethyl acrylate as shown in **Scheme 23** demonstrates the use of both $Pd(OAc)_2$ and $Pd(CH_3CN)_2Cl_2$ with XS phosphine ligand and Et_3N to be unsuccessful in a coupling yielding desired product **28**.

Scheme 23



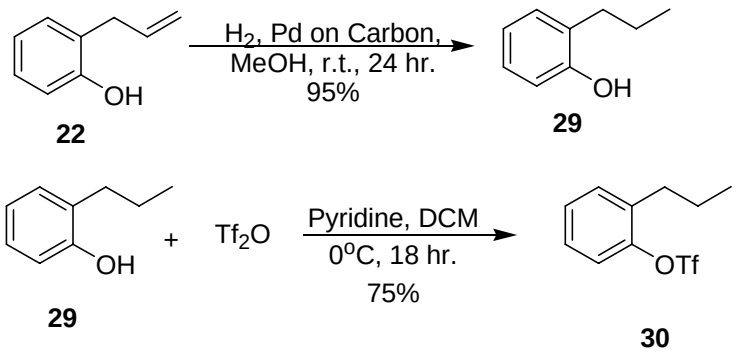
23 **28**

As was the case in the tandem reactions run previously, starting material was recovered with no observation of **28**. This confirms the unreactivity of the 2-allylaryltriflate for standard Heck coupling conditions using standard Heck conditions.

The coordination hypothesized in **Scheme 22** certainly could stabilize the intermediate and make it uncreative towards alkene partners. Further, it would tie up the catalyst resulting in only trace amounts (10 mol%) of the Ar-H being observed upon workup, whereby protonation of the C-Pd bond would result in C-H incorporation. Given that Pd could potentially coordinate with the allyl group intramolecularly, one might consider an undesired intramolecular Heck reaction from **27**. Although the geometry exist to allow coordination intramolecularly, it is obvious after modeling that the transition state leading to alkene insertion between the C-Pd bond would be far to strained to be feasible. Further, this side product was never observed in any reactions throughout the project.

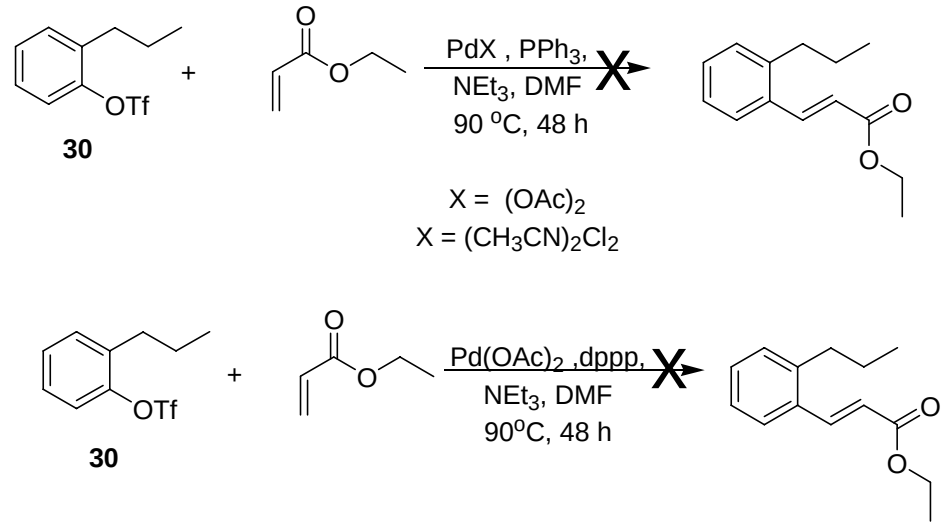
To test the hypothesis of intramolecular olefin coordination, the hydrogenated version of the triflate was explored. An investigation looking at 2-propylphenyltriflate (**30**) would also address the steric effects of ortho-substituted aryltriflate reactivity. The material was therefore synthesized from commercially available 2-allylphenol(**22**). 2-allylphenol (**22**) was catalytically hydrogenated with 10 mol% Pd/C in methanol under a hydrogen atmosphere via balloon for 24 hours yielding 95% of the hydrogenated phenol **29**. Phenol **29** was then reacted with triflic anhydride following the same procedure as in **Scheme 19** to yield 75% of aryl triflate **30**.

Scheme 24



With the trifluoromethanesulfonic acid 2-propyl-phenyl ester (**30**) available, acrylate studies varying the Pd precatalyst and ligand choice were made based upon common reactions found in the literature[14]. **Scheme 25** demonstrates variations which yielded no desired product, and recovery of starting material.

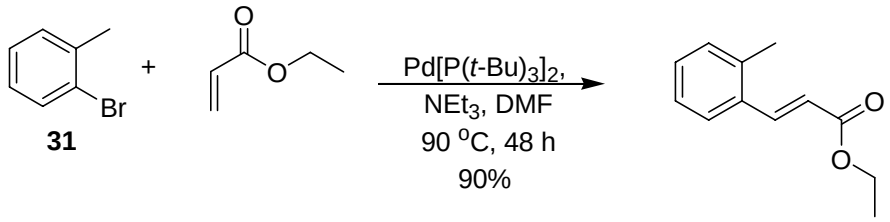
Scheme 25



While exploring the reactivity of the triflates, it was proposed that halides such as bromide could yield positive results. Commercially available *o*-bromotoluene was reacted with ethyl acrylate utilizing a commercially available bis-tri-*t*-butyl phosphine palladium catalyst.

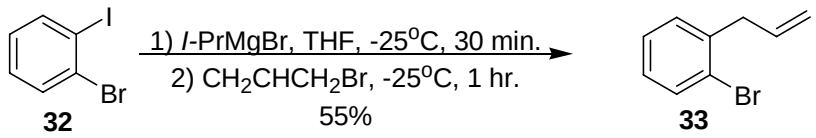
This palladium source has been shown by Gregory Fu to be useful for bromides and chlorides[20,21]. Further, this catalyst is a direct source of Pd(0) and thus eliminating any possibility of not generating the Pd(0) *in stitu*. It is thought that bulky electron-rich ligands on palladium are better for reactions in which oxidative addition is typically an issue such as chlorides and some bromides. Conditions including the hindered electron-rich phosphine ligand yielded 90% of the desired Heck coupled product with the acrylate as demonstrated in **Scheme 26**.

Figure 26



Based upon the success of the aryl bormide **31**, a variety of conditions were explored in an attempt to couple the 1-allyl-2-bromo-benzene (**33)** with the cyclic vinylogous ester **26**. It was thus necessary to make **33**. 1-allyl-2-bromo-benzene can be afforded from Grignard chemistry. Addition of *i*-propyl-magnesium bromide to commercially available *o*-bromo-iodobenzene (**32**) at -25 °C in THF followed by addition of allylic bromide after 30 minutes yielded 55% of the alkylated product **33** after 1 hour as demonstrated in **Scheme 27.**

Figure 27



With **33** in hand, several reactions were carried out to attempt the desired Heck coupling. These conditions and results are summarized below in **Scheme 28** and **Table 1**.

Scheme 28

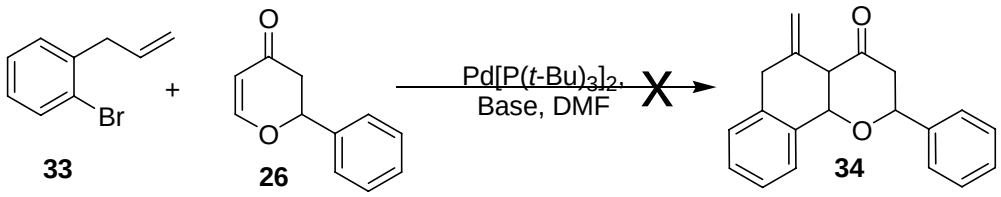


Table 1

Entry	Base	Temperature (^{o}C)	Time (Hr.)	Yield
1	Et_3N	80	24	Recovered **26** not **33**
2	Et_3N	120 μW	2	RSM, Low mass of **33**
3	$(i\text{-pr})_2NEt$	120 μW	2	RSM, Low mass of **33**
4	Cy_2NEt	120 μW	2	RSM, Low mass of **33**

As one can see from **Table 1**, in all cases, starting material was recovered with low recovery of bromide **33.** This might suggest that oxidative addition was occurring with subsequent Ar-H formation via a proton source such as trace water (given the scale of the reaction, trace water could result in conversion of Ar-Pd to Ar-H). One other explanation stems from recent literature whereby amine bases have been shown to be a hydride source in palladium cross coupling reactions[22]. Due to the small scale of these screening reactions it is quite possible that such trace amounts of Ar-H via a wet reaction would not be able to be observed by NMR in the crude mixture or be isolated by flash chromatography.

Due to lack of results of the tandem reaction, a model study utilizing *o*-bromotoluene (**31**) was considered. This compound was chosen due to similar steric hindrance of the ortho

substitutuent without the olefin interference of the allyl group of **33**. It is known that the A value of a methyl is 1.74 while that of an ethyl is 1.79[23]. It is also known that atoms further from the branch point have less effect, and thus it is felt that the A value of an allyl group would be closer to the ethyl A value, than the ethyl A value is to the methyl A value. Because ethyl and methyl are fairly similar, it is arguable that the relative steric difference in *o*-bromotoluene(**31**) and **33** is negligible. Therefore, any differences in reactivity would be only strongly influenced by electronic differences rather than sterics. A screening was thus explored and shown in **Scheme 29** and **Table 2.**

Scheme 29

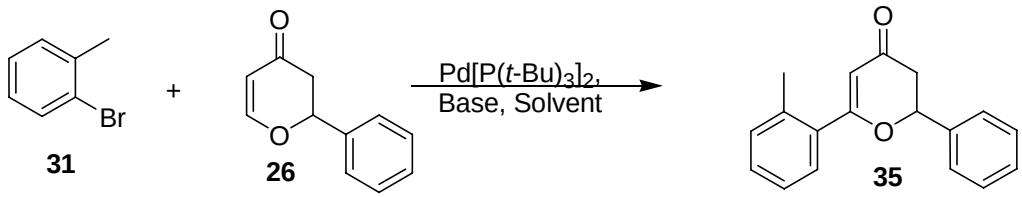


Table 2

Entry	Solvent	Base	Temperature (°C)	Time (Hr.)	Yield
1	DMF	Et_3N	80	24	7% Low Mass Balance
2	DMF	Et_3N	80 then 120, μW	1 then 1	RSM Low Mass Balance
3	DMF	$(i\text{-pr})_2Net$	80 then 120, μW	1 then 1	18%, RSM
4	CH_3CN	Cy_2NMe	120μW	1	<5%, RSM

Entry 1 and **2** of **Table 2** utilize DMF and triethylamine while varying temperature, time and method. Entry **1** was heated in an oil bath to yield 7% of the desired product noticeable by TLC and confirmed by NMR. This entry, amongst others confirmed the position of reactivity of

the vinylogus ester to yield C-C bond formation at the β-Carbon as predicted. It is generally known that the microwave can greatly decrease reaction time, and it was found that microwave Heck reactions yield much faster reaction times. **Entries 2-4** thus utilize microwave heating varying base and solvent. **Entry 3** demonstrates the hindered hunig's base to yield 18% of the desired product. It is known that choice of base has a large impact on the efficiency of the process. One explanation is that the base can coordinate to palladium, and thus more hindered base will be less likely to coordinate, and the ability of Pd to carry out the cycle without amine interference would be increased with more hindered bases that are unable to interfere and stabilize the palladium species. One other interesting observation to be made from this set is the difference between **Entries 3** and **4**. Cy_2NMe and Hunig's base are similar in steric bulk, but yet **Entry 4** yielded less than 1/3 the amount of product than **Entry 3**. It is felt that the stronger polarity of acetonitrile contributed to this lower yield, as more polar solvents can more heavily influence Pd-L interactions as well as the strength of the base used.

It is known that additives can commonly influence reactivity of the Heck reaction[11]. Tetrabutylamonium chloride (TBAC) has been shown in the literature to enhance reactivity of the Heck reaction[24]. It is unclear exactly how TBAC's contribution enhances the reactivity, however one explanation is that it is thought that TBAC increases the concentration of chloride – known to be a stabilizing ligand on palladium. In this way TBAC is thought to increase longevity of the palladium catalyst as well as potentially make it a more reactive catalyst for olefin insertion. With this knowledge in hand, 1.0 equivalent of TBAC was added and conditions were surveyed as demonstrated in **Scheme 30** and **Table 3**.

Scheme 30

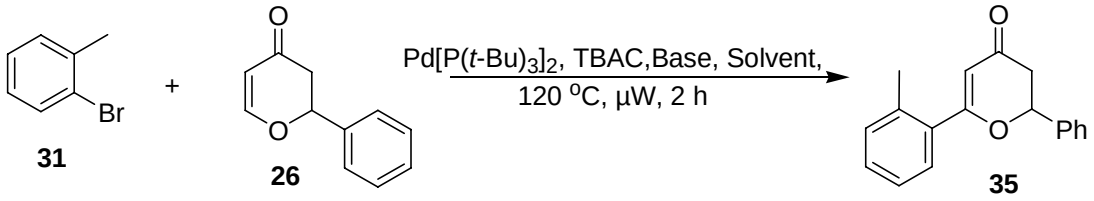


Table 3

Entry	Solvent	Base	Yield
1	DMF	$(i\text{-Pr})_2NEt$	48%
2	CH_3CN	$(i\text{-Pr})_2Net$	27%
3	Dioxane	$(i\text{-Pr})_2Net$	22%
4	DMF	Cy_2NMe	48%
5	DMF	Et_3N	19%

Entry 1 of **Table 3** clearly indicates that the presence of TBAC greatly increases the yield of the desired product **35**. From the Table, it can be concluded that DMF and Dioxane with hindered amines such as Hunig's base and dicyclohexylmethylamine clearly yield the best results when TBAC is added to the reaction mixture.

A temperature study was conducted to determine if more mild conditions could be employed. **Scheme 31** and **Table 4** demonstrate that below 100 °C, little reactivity occurs.

Scheme 31

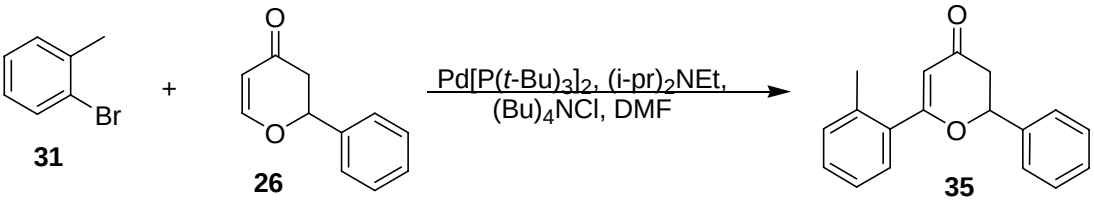
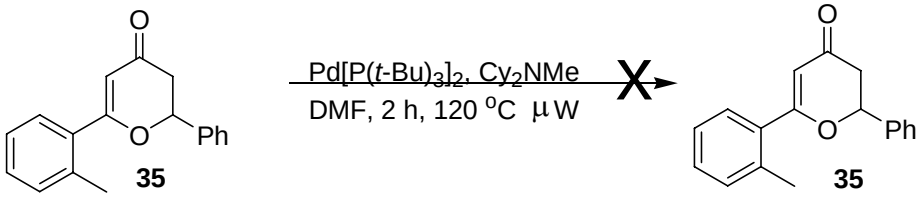


Table 4

Entry	Time	Temperature (^{o}C)	Ratio by NMR (35:26)	Isolated Yield
1	4 days	r.t.	NR	NR
2	2 Hr.	60, μW	1:100	---
3	2 Hr.	80, μW	1:8	---
4	2 Hr.	100, μW	13:1	41%
5	19 Hr.	100 Oil Bath	--	52%

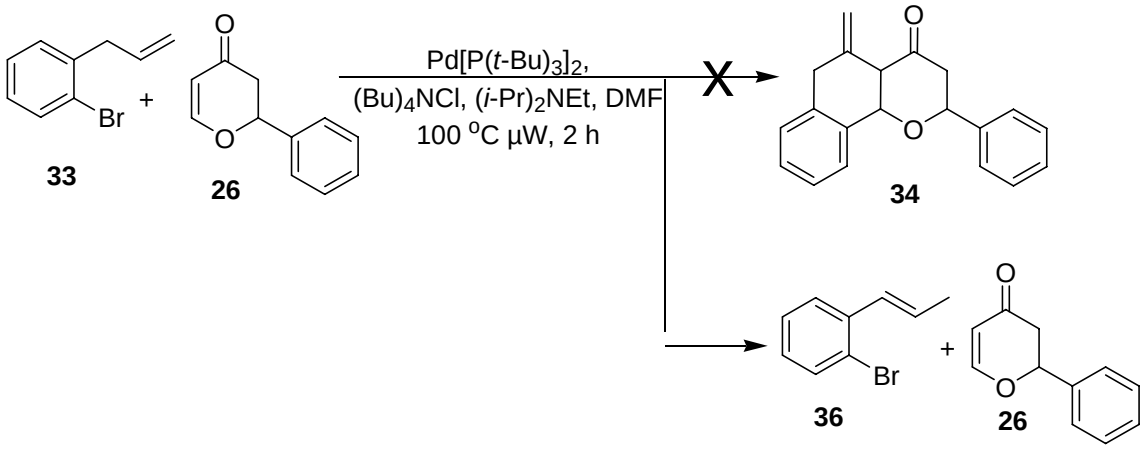
Based upon **Table 4** one can clearly see that temperatures greater than 80 ^{o}C were required to give notable conversion. **Entry 5** showed no product after 2 hours, but when let run over night, resulted in the 52% yield as reported providing evidence toward the idea that the microwave greatly reduces reaction times with comparable yields. **Scheme 32** demonstrates that temperatures of 120 ^{o}C for 2 hours results in total decomposition of the product. NMR of the crude reaction mixture revealed an indeterminable mess, and no recovery of **35**. This therefore implies that a particular and narrow temperature range is required for this reaction. Further, it serves as an explanation for low yields. It is evident that thermal decomposition of the product is clearly competing with product formation.

Scheme 32



With the knowledge gained from the model system and those optimized conditions employed, the tandem reaction was again tried as demonstrated in **Scheme 33**.

Scheme 33



As shown in **Scheme 33**, no product was seen by TLC nor isolated. Interestingly, **33** was recovered as the conjugated isomer **36**. It is unclear by what mechanism this occurred, however it can be speculated that trace amounts of Pd-H could potentially isomerizes the double bond into conjugation with the aromatic ring. Further, because mostly aryl bromide, rather than Ar-H was recovered, this again leads one to believe that either the catalyst was tied up in an intermediate such as **27**, or the oxidative addition was not occurring due to electronic effects of the allyl olefin. The vinylogous ester **26** was recovered confirming that olefin insertion did not occur. It is thus clear from these results that vinylogous esters are poor olefins for Heck couplings to insert into a stabilized o-allylAryl-Pd complex via stabilization of the Pd by the adjacent *o*-allyl olefin.

IV. Conclusions

Reactions of *o*-substituted bromides were able to be successfully reacted in a Heck coupling with a cyclic vinylogous ester structure in moderate yields. Although factors such as base and solvent played a crucial role in improvement of yield, the use of a bulky electron-rich ligand on palladium was required to achieve any product formation. Further, the addition of TBAC played the most significant role in obtaining a noteworthy yield of the desired product. It was observed that triflates seemed to be a poorer substituent for oxidative addition when utilizing a bulky electron-rich phosphine ligand; contrary to the traditional order of reactivity whereby one would expect triflates to be more activated for oxidative addition than bromides.

From these results it becomes clear that a Heck reaction with the vinylogus ester structure is quite finicky, requiring a unique compilation of base choice, solvent choice, Pd-ligand choice, and additives in order to achieve reactivity. Further, a high degree of substrate dependence deems this methodology impractical as a useful method for the outlined tandem sequence. However, it was able to be shown that the reactivity of vinylogous esters in Heck reactions is at the β-carbon, which is previously unprecedented in the literature.

Future directions would be to explore the reactivity of more vinylogous esters such as Chromone and other substitutions neighboring the vinylogous ester that might influence the electronic environment of the olefin to gain a more complete picture of the unique reactivity of vinylogous esters. Further, additional studies as to the cause for interference of the *o*-allyl group would be useful. In particular, reactions of *o*-allylphenylbromide with electron withdrawing and electron donating olefins might gain insight as to the stabilizing effects of the *o*-allylaryl-Pd species.

V. Experimental

Unless otherwise indicated, all starting materials were obtained from commercial sources and used without further purification. Dichloromethane (DCM), hunigs base ((i-Pr)$_2$Net), pyridine, dicyclohexylmethylamine (Cy_2NMe), and Trimethylsilyl chloride (TMSCl) were freshly distilled from Calcium hydride and stored under Nitrogen. Acetonitrile, Dioxane, Tetrahydrofuran (THF), and Dimethylformamide (DMF) were passed through two columns of neutral alumina and stored under Argon. Triflic Anyhydride (Tf_2O) was freshly distilled from P_2O_5. All starting material reactions were run under Nitrogen atmosphere unless otherwise specified, while all heck reactions were run under Argon atmosphere. ^{1}H NMR were collected on a Varian 450 MHz device in $CDCl_3$ unless otherwise noted.

General procedure for the synthesis of aryl triflates from phenols Illustrated by a procedure for Trifluoro-methanesulfonic acid 2-allyl-phenyl ester (**23**). A 100 mL roundbottom flask was first charged with 20 mL of dichloromethane and 20 mL of pyridine. To this was added 5.37g (40 mmol, 1.0 eq.) of 2-allylphenol. The flask was cooled to 0 ^{o}C and 8.12 mL (48 mmol,1.2 eq.) was added slowly dropwise. The reaction was stirred and let warm to r.t. after 2 hours, and stirring was continued for 16 hours. The reaction was quenched with 40 mL of water, placed into a separatory funnel and (3X) extracted with ethyl acetate. The organic layers were combined and washed with 5% HCl, followed by a saturated sodium bicarbonate wash and brine wash. The organic layer was dried over magnesium sulfate and then concentrated to afford 98% of the title compound as a light yellow oil. ^{1}H NMR (450 MHz, $CDCl_3$) δ = 7.35-7.27 (m, 4H), 5.92 (ddt, 1H), 5.15 (m, 2H), 3.49 (3.49, 2H).

trans-1-Methoxy-3-trimethylsiloxy-1,3-butadiene –Danishefsky's Diene (**25).** A Flame dried 250 mL flask was charged with 71.6 mL (0.51 mol, 1.1 eq.) of triethylamine and 2.0 g (3 mol%) freshly fused zinc chloride. The solution was stirred for 1 hour to allow suspension in the amine. 50 mL (0.50 mmol, 1 eq.) of *Trans*-4-methoxy-3-buten-2-one and 150 mL of toluene was then added. 63.5 mL (1.0 mmol, 2 eq.) of TMS-Cl was then slowly added as the reaction exothermed. After 30 minutes, the reaction was heated via oil bath to 40 ^{o}C and let stir for 12 hours. The solution was then cooled to r.t. and added to 1 L of diethylether. This was then filtered, and the filtrate was concentrated resulting in a brown oil. The oil was distilled at 55 ^{o}C to yield 52% of the title compound. ^{1}H NMR (450 MHz, $CDCl_3$) δ = 6.67 (d, 1H), 5.21 (d, 1H), 3.93 (broad d, 2H), 3.44 (s, 3H), 0.09 (s, 9H).

2-phenyl-2,3-dihydro-pyran-4-one **(26)**. 494 mg (3.61 mmol, 1 eq.) of freshly fused zinc chloride was placed in a N2 flushed, flame dried 10ml flask. To this, 5 ml of THF was added. Once the zinc chloride had dissolved, 385 mg (3.62 mmol, 1 eq.) of benzaldehyde was added followed by addition of 100 mg (5.80 mmol, 16. Eq.) of Danishefsky's diene. This mixture was stirred at room temperature for 2 days. The reaction was quenched with water and then worked up by extraction with Et2O (3x), washed twice with 1N HCl, followed by a saturated NaHCO3 wash and finally washed with saturated sodium chloride. The organic layer was then dried over magnesium sulfate and concentrated under reduced pressure to afford a crude yellow oil. The material was then purified by flash chromatography (3:1 pentane: Et2O) to elude 69% of the title compound as a yellow oil. ^{1}H NMR (450 MHz, CDCl3) δ 7.49 (dd, 1H) 7.41 (m, 5H) 5.53 (dd, 6.06 Hz, 1H) 5.44 (dd, 1H) 2.93 (q, J = 14.48, 16.82 Hz, 1H) 2.67 (ddd, 1H).

2-propylphenol (**29**). A 200 mL flask was freshly charged with 50 mL of MeOH and 5.32 g (10 mol%) of Pd/C. 65.26 mL (0.5 mol, 1 eq.) of 2-allylphenol was then added to the solution. The atmosphere was purged with hydrogen gas, and a large hydrogen filled balloon was fixed atop the septum pierced by a needle such that hydrogen could be delivered to the system. The reaction was left to stir for 24 hours. The solution was filtered through a plug of celite to remove the Pd/C. The solution was concentrated and purified by flash chromatography (4:1 Hex: EtOAc on Silica gel) to afford 95% of the title compound as a clear oil. ^{1}H NMR (CDCl3, 450 MHz) δ = 7.12-7.0 (m, 2H), 6.84-6.75 (m, 2H), 2.56 (t, 2H), 1.58 (tt, 2H), 0.95 (t, 3H).

1-allyl-2-bromo-benzene (**33**). Di-isopropylmagnesium bromide was freshly titrated with I_2 just prior to setting up the reaction. A 10 mL flask was flame dried and charged with 3 mL of THF along with 45.4 μL (0.35 mmol, 1 eq) of *o*-bromo-iodobenzene. The flask was then cooled to -25 ^{o}C via regulated dry ice / acetone bath. 1.0 equivalent of the Grignard was then added slowly dropwise over 10 minutes. The reaction was then carefully maintained between -30 to -20 ^{o}C for 30 minutes. 153 μL (1.77 mmol, 5.0 eq.) of allyl bromide was then added and was left to stir for 1 hour maintaining the range indicated around -25 ^{o}C. The reaction as then allowed to warm to r.t. over an hour, quenched with 10 mL of water, and 3X extracted with diethyl ether. The ether layers were combined and washed with brine and concentrated to give a crude clear oil. The crude oilw as purified by flash chromatography with pure hexanes to afford 38 mg (55%) of the title compound. ^{1}H NMR (450 MHz, CDCl3) δ = 7.56-7.48 (m, 1H), 7.28-7.21 (m, 2H), 7.11-7.05 (m, 1H), 5.97 (ddt, 1H), 5.09 (m, 2H CHCH2), 3.52 (dt, 2H).

General Procedure of Heck reactions involving Pd(II) precatalyst: A 25 mL flask was first flame dried and Argon flushed. The flask was then charged with specified solvent such that the concentration of the aryl halide or triflate was 0.1M. The 10 mol% Palladium catalyst was

added, and to this 30 mol% of $PPh_3$was added. 1.0 eq. of each heck coupling partner was then added followed by 3.0 eq. of the desired base. The reaction as heated and stired as indicated. After cooling, the reaction was quenched with water, and 3X extracted with Ethyl Acetate. The organic layers were combined and washed with 1N HCl followed by sat. sodium bicarbonate, then brine. The organic solution was then dried over Magnesium sulfate and concentrated to yield the crude oil. The components of the mixture were then separated by flash chromatography utilizing 4:1 Hexane : Ethyl Acetate. Fractions were then characterized by ^{1}H NMR.

General Procedure of Heck reactions involving $Pd[(t\text{-}Bu)_3]_2$. A 25 mL flask was first flame dried and Argon flushed. The flask was then charged with specified solvent such that the concentration of the aryl halide or triflate was 0.1M. The 10 mol% Palladium catalyst was added 1.0 eq. of each heck coupling partner was then added followed by 3.0 eq. of the desired base. The reaction as heated and stired as indicated. After cooling, the reaction was quenched with water, and 3X extracted with Ethyl Acetate. The organic layers were combined and washed with 1N HCl followed by sat. sodium bicarbonate, then brine. The organic solution was then dried over Magnesium sulfate and concentrated to yield the crude oil. The components of the mixture were then separated by flash chromatography utilizing 4:1 Hexane : Ethyl Acetate. Fractions were then characterized by ^{1}H NMR.

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Vita

Seth Chase Alexander was born in Kermit, Texas on January 3, 1986 to Gregory Guy and Mary Ellen Alexander. After graduating from Fredericksburg High School, Fredericksburg, Texas, in 2004, he attended The University of Texas at Austin. During the course of his undergraduate education, he was first under the advisement of Dr. Tom J. Mabry for his first year, followed by Dr. Stephen F. Martin for the remaining three years. He also was fortunate to be employed by Max Planck for a summer internship as a DAAD RISE fellow, as well as by Pfizer as a summer undergraduate research fellow. In August, 2008 he will begin graduate studies at Yale University in pursuit of a Ph.D. in Chemistry.

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